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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,533	12/13/2005	Anna Fernandez Serrat	3378-0101	6463

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EXAMINER	
MURRAY, JEFFREY H	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
03/19/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/560,533	FERNANDEZ SERRAT ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-14 and 30-45* is/are pending in the application.

4a) Of the above claim(s) *30-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-14 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/17/2006 & 6/30/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an election from a restriction requirement filed on December 29, 2008. There are twenty-nine claims pending and fourteen claims under consideration. Claims 1 and 15-29 have been cancelled. Claims 30-44 have been withdrawn. This is the first action on the merits. The present invention relates to new benzamides acting as PPARγ and PPARγ/PPARδ modulators, as well as to processes and intermediates useful for their preparation, and to pharmaceutical compositions containing them. Election was made **without** traverse in the reply filed on December 29, 2008. Therefore this restriction is considered proper and thus made **FINAL**.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority. The current application, 10/560,533, filed on December 13, 2005, is a national stage entry of application PCT/EP04/06330, filed on June 11, 2004, which claims foreign priority to Spanish Application P200301461, filed on June 13, 2003.

Specification

3. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

4. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

Claim Objections

5. Claims 2-14 and 45 are objected to because of the following informalities:

Claims 2-14 and 45 are objected to for containing non-elected subject matter within the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2-14 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds or pharmaceutically acceptable salts, does not reasonably provide enablement for any polymorphs and mixtures thereof or pharmaceutically acceptable solvates within the broad Claim 45. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (United *States v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant*. The Applicant has demonstrated within the application how to make the various benzyloxy-substituted benzamides. However, there is no working example of any polymorphs or solvates. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However...there is no evidence that such compounds exist...the examples of the '881 patent do not produce the postulated compounds...there is...no evidence that such

compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

The applicant has not shown any useful data or guidance that would define a particular polymorph that would be biologically active. The applicant has inferred within the specification that any "morphological forms of the compound" would be acceptable. This can clearly not be the case. A contrasting example to this would be chloramphenicol palmitate (CAP). CAP exists in a form A and B. The metastable "form B" of CAP has an eight-fold higher bioactivity than "form A." Yet if "form B" is administered to humans, it can cause potentially fatal side effects. (Chawla et. al.; Current Research & Information on Pharmaceutical Science, 2004, 5(1), p. 9-10). Also a variety of dosage forms are available for pharmaceutical products. (Newman et. al.; Drug Discovery Today (2003), 8(19) p. 899, col.2, Box 1.) A polymorph can affect the key solid-state parameters. For example, the drug substance in a tablet formulation will be significantly different than those for an oral suspension or inhalation product. (Newman et. al.; p. 898, p. 898, col.2, Para.1)

2) *Unpredictability in the art*. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Chemistry is unpredictable. See In Re Marzocchi and Horton 169 USPQ at 367

paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)." Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.
>
> The scope of "solvate" and "hydrate" is not adequately enabled or defined.

Applicants provide no guidance as how the compounds are made more active *in vivo*.

Solvates cannot be predicted and there fore are not capable of being claimed if the

applicant cannot properly enable a particular solvate.

> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates. Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.

Morphological forms of the compound, or "polymorphs" are the ability of a substance to exist in two/more crystalline phases that have different arrangement and/or conformation of molecules in a crystal lattice.

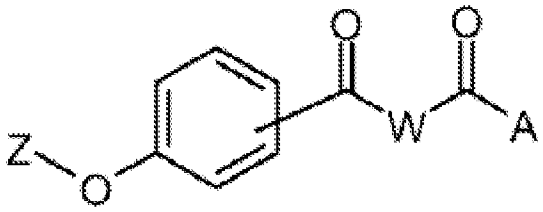
Screening of pharmaceuticals early on in drug discovery to find out all possible solid forms has significant connotations. (Chawla et. al.; p. 9, col.2, para.1) When designing formulations, it is imperative to know which crystal form of a drug is present at the various stages of a process. "It may be possible that if one polymorph of an active pharmaceutical ingredient, or API, is responsible for activity, another form may be less active, inactive, toxic, or have some other properties of interest." (Chawla et. al.; p. 9, col.2, para.3)

Polymorphs can exhibit many types of differences in their physical properties such as a) packaging; b) thermodynamic; c) spectroscopic; d) kinetic; e) surface; and, f) mechanical properties. (Chawla et. al.; See Table 1, p. 10) These properties offer scientists the opportunity to manipulate bioavailability. It is important to determine if there are phase transformations occurring during processing as well as what crystal form is present in the final drug product. (Newman et. al.; p. 898 col.2, Para.3.)

3) *Number of working examples*. The compound core depicted with specific substituents represents a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any polymorphs or solvates in the present application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims
must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Scope of the claims*. The scope of the claims involves all of the tens of thousands of compounds having the Formula (I):



Where Z is a benzyl group; W is –NH-CH(E)- where E is –G-I-J-K- and I is a phenyl or cyclohexyl ring, thus, the scope of claims is very broad.

5) *Nature of the invention*. The present invention relates to new benzamides acting as PPARγ and PPARγ/PPARδ modulators, as well as to processes and intermediates useful for their preparation, and to pharmaceutical compositions containing them.

6) *Level of skill in the art*. The artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions or treating the diseases mentioned.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

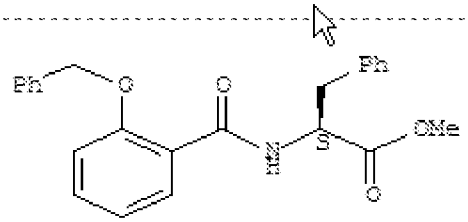
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 2, 3, 12-14 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Divanyan, et. al., Khimiko-Farmatsevticheskii Zhurnal (1978), 12(9), 45-8.

The compound in the prior art is represented as:

RN 68939-37-7 CAPLUS
CN L-Phenylalanine, N-[2-(phenylmethoxy)benzoyl]-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



Whereby Z is a benzyl group; A is a OR1 group, where R1 is a hydrogen; W is a –NH-CH(E)- group, where E is –G-I-J-K- and G is a CH_2, I is a phenyl ring, J is a bond and K is a hydrogen. This prior art document is currently being delivered to the patent office and will be forwarded on to the applicants as soon as it is received.

Conclusion

10. Claims 1-14 and 45 are rejected.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on Mon.-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey H Murray/
Patent Examiner , Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624